REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections set forth in the Office action dated July 31, 2001 are respectfully requested. Applicants petition the Commissioner for a 3-month extension of time. A separate petition accompanies this amendment.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page(s) is/are captioned "**Version with Markings to Show Changes Made**."

I. Amendments to the claims

The preambles of claims 1 and 10 have been amended to describe a method for "modulating hematopoietic stem cell differentiation". Support for this amendment can be found, for example, on page 4, lines 15-17. Claims 1 and 10 have additionally been amended for clarity and to clarify that the antisense oligomers are additionally or alternatively able to effect a slowing or diminution of the growth of cells characterized by a loss of growth control. Support for this amendment can be found on page 8, lines 38-40.

Claims 8 and 9 have been amended for clarity.

Claim 17 has been amended to recite an antisense oligomer with a substantially uncharged backbone. Support for this amendment can be found, for example, on page 10, lines 28-29.

Claim 18 has been amended for consistency with claim 17.

No new matter has been added by these amendments.

II. Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-16 and 20 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to

enable one skilled in the art to make and use the invention without undue experimentation. Applicants respectfully traverse the rejection for the following reason.

A. Analysis

The first paragraph of 35 U.S.C. §112 requires that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention without undue experimentation (e.g., *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir., 1991).

Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples (*In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed Cir. 1993).

The enablement requirement is met if the description enables any mode of making and using the claimed invention (*Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 20 USPQ2d 1300 (Fed. Cir. 1991).

As noted above, Applicants have amended the claims to be directed to compositions and methods for modulating hematopoietic stem cell differentiation using one or more antisense oligomers directed to an mRNA preferentially expressed in stem cells.

Example 2 sets forth an example of the claimed method. Specifically, the study in Example 2 shows that hematopoietic stem cells exposed to an antisense oligomer directed to an mRNA expressed in the stem cells was effective to decrease the number of high proliferative potential colony forming cells (HPP-CFC) cells, indicating modulation of the stem cell differentiation. In the study, cells enriched for long term repopulating hematopoietic stem cells (LTR-HSC) were grown in medium with or without antisense oligomers and assayed after 5 days for HPP-CFC

formation. The assay results indicate that exposure of the cells to the mRNA preferentially expressed in LTR-HSCs (Example 1), EVI-1 antisense, yielded a decrease in HPP-CFC cells, which indicates differentiation of hematopoietic stem cells.

In light of the claim amendments and the teaching in the specification, Applicants submit that the present claims satisfy the enablement requirement of §112, first paragraph and respectfully request that the rejection be withdrawn.

III. Rejection under 35 U.S.C. §112, second paragraph

Claims 4, 5, 8, 13, 14, and 18-20 were rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. Specifically, the Examiner objected to the language "substantially uncharged" in claims 4, 13 and 18. The Examiner further objected to claims 5 and 14 allegedly for reference to structures which are presented in figures.

According to the M.P.E.P. §2173.05(b), "The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite...Acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed, in light of the specification." Specific to the term "substantially", M.P.E.P. §2173.05(b) states, "The term "substantially" is often used in conjunction with another term to describe a particular characteristic of the claimed invention. It is a broad term. In re Nehrenberg, 208 F.2d 161, 126 USPQ 383 (CCPA 1960). The court held that the limitation "to substantially increase the efficiency of the compound as a copper extractant" was definite in view of the general guidelines contained in the specification."

Applicants direct the Examiner to page 10, line 27 through page 11, line 34 where exemplary uncharged antisense oligonucleotides are discussed. Applicants submit that a person of skill in the art would understand what "substantially uncharged" intends in light of the teaching in the specification. Accordingly, withdrawal of the objection to this term is requested.

With regard to the reference to structures presented in the Figures, Applicants submit that the claim language as presented is the most concise way to describe the metes and bounds of the claimed invention. Applicants are willing to amend the claim language if the Examiner deems that the amendment of the claims is necessary, and the Examiner is invited to suggest alternative claim language.

IV. Rejection under 35 U.S.C. §102

Claims 17 and 19 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mitani *et al.* (*Blood*, 1994, 84(10):229a). This rejection is respectfully traversed for the following reason.

A. The Invention

The present invention as embodied in amended claim 17 relates to a composition comprising an antisense oligomer with a substantially uncharged backbone directed to a sequence spanning the mRNA translational start codon of a gene preferentially expressed in stem cells.

B. The Prior Art

MITANI ET AL. describes an AML1/EVI-1 fusion protein which is a chimeric transcription factor including a runt homology domain from AML1 and two zinc finger domains from EVI-1 and an acidic

domain from the EVI-1 as a transcriptional activation domain. Mitani *et al.* also describes the use of a synthetic antisense oligonucleotide to evaluate the effects of the AML1/EVI-1 fusion protein on cell growth of SKH1 cells. The oligonucleotide spans the junction point between AML1 and EVI-1.

C. The Legal Standard

The standard for lack of novelty, that is, for anticipation, is one of strict identify. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986); *In re Donohue*, 766 F2d 531, 226 (USPQ 619, 621 (Fed. Cir. 1985). To anticipate a claim for a patent, a single prior source must contain all its essential elements.

D. Analysis

Mitani *et al.* fail to show an antisense oligomer with a substantially uncharged backbone. In fact, nowhere does Mitani *et al.* discuss the oligomer backbone. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102 be withdrawn.

V. Rejection under 35 U.S.C. §103

Claims 17-19 were rejected under 35 U.S.C. §103 as allegedly obvious over Mitani *et al.* in view of Baracchini *et al.* (U.S. Patent No. 5,801,154).

A. The Present Invention

The present invention is described above.

B. The Prior Art

MITANI ET AL. is described above.

BARACCHINI ET AL. describe antisense strategies against multidrug resistance-associated protein, or MRP. The reference describes more than 20 classes of oligomer backbone variations, with numerous structural variations for each class of backbone given. (Col. 6-8). However, the only oligomers shown to be effective all have charged phosphorothioate backbones (Tables 1-4).

C. Analysis

The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). Obviousness requires some logical reason for combining the references at hand; otherwise, the use of the references will entail prohibited hindsight (e.g., Ex parte Stauber 206 USPQ 945; In re Adams 148 USPQ 742; In re Imperato 179 USPQ 730).

The present invention as embodied in claims 17-19 relates to a composition comprising an antisense oligomer with a substantially uncharged backbone that is directed to a sequence spanning the mRNA translational start codon of a gene preferentially expressed in stem cells.

Mitani *et al.* is completely silent as to the nature of the oligonucleotide backbone. Thus, Mitani *et al.* provides no guidance for modifying the backbone.

Baracchini *et al.* disclose hundreds of possible oligomer backbones for use in antisense strategies against multidrug resistance-associated protein. Nowhere does Baracchini *et al.* provide any guidance for selection of a substantially uncharged backbone from the hundreds of possibilities disclosed.

To modify the oligonucleotide of Mitani *et al.* with a backbone of Baracchini *et al.* for use with an mRNA translational

start codon of a gene preferentially expressed in stem cells is to engage in hindsight reconstruction. There is simply nothing in the references that, in the absence of the Applicants' own invention, would lead the Examiner to "pick and choose" from the hundreds of disclosed backbones.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

VI. Conclusion

In view of the foregoing, Applicants submit that the claims pending in the application comply with the requirements of 35 U.S.C. §112 and patentably define over the prior art. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

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Appl. No. 09/684,061

VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A method of [treating a human cancer patient]modulating hematopoietic stem cell differentiation, comprising:

[administering to the patient,]providing one or more antisense oligomers directed to an mRNA preferentially expressed in stem cells, [wherein said administering is] effective to achieve an (i) increase in the number of lineage committed progenitor cells and their progeny [in the peripheral circulation of the subject], and/or (ii) effect a slowing or diminution of the growth of [cancer cells or a solid tumor]cells exhibiting a loss of growth control, or a reduction in the total number of [cancer cells or total tumor burden in the patient]such cells.

8. (Amended) The method according to any one of claims 1 to 7, wherein said one or more antisense oligomers is [administered]provided to a subject in an amount sufficient to result in a peak blood concentration of at least 200-400 nM.

9. The method according to claim [1]8, wherein said [administering]providing is carried out at a concentration of said one or more antisense oligomers, and for a period of time sufficient to increase the number of lineage committed progenitor cells and their progeny in the peripheral circulation of the [patient]subject at least four-fold relative to the number of lineage committed progenitor cells and their progeny present in the peripheral blood of the [patient]subject prior to administration of said one or more antisense oligomers.

10. (Amended) A method of [treating a human cancer patient]modulating hematopoietic stem cell differentiation, comprising:

(a) obtaining a stem cell-containing cell population from a subject;

(b) treating the cell population in manner effective to enrich the cell population for stem cells; and

(c) exposing the enriched stem cell population, *ex vivo* to one or more antisense oligomers directed to an mRNA preferentially expressed in stem cells, under conditions effective to (i) to increase the population of lineage committed progenitor cells and their progeny in the peripheral circulation of the subject, and/or (ii) effect a slowing or diminution of the growth of [cancer cells or a solid tumor]cells exhibiting a loss of growth control, or a reduction in the total number of [cancer cells or total tumor burden in the cell population]such cells; and

(d) infusing the antisense oligomer-treated cell population into said [human cancer patient]subject.

17. (Amended) A composition comprising an antisense oligomer characterized by a backbone which is substantially uncharged, where said oligomer is directed to a sequence spanning the mRNA translational start codon of a gene preferentially expressed in stem cells.

18. (Amended) The composition according to claim 17, wherein said antisense oligomer is characterized by,

[(a) a backbone which is substantially uncharged;]

[(b)](a) the ability to hybridize with the complementary sequence of a target RNA with high affinity at a Tm greater than 50°C;

[(c)](b) nuclease resistance; and

[(d)](c) the capability for active or facilitated transport into cells.